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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 28

Serial Number: 07/649342
Filing Date: 02/01/91
Appellant(s): Hughes B. De The et.al.

MAILED
AUG 24 1994
GROUP 180

94-1465
Kenneth J. Meyers
For Appellant

EXAMINER'S ANSWER

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This is in response to appellant's brief on appeal filed 7 July of 1993.

(1) Status of claims.

The statement of the status of claims contained in the brief is correct.

(2) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The amendment after final rejection filed on 15 April of 1993 has been entered.

(3) Summary of invention.

The summary of invention contained in the brief is correct.

(4) Issues.

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

The Petkovich et.al. reference clearly teaches a DNA encoding a retinoic acid receptor which is structurally similar to Appellants' RAR-ß and teaches the presence and partial nucleotide sequence of a human genomic DNA which is structurally related to the DNA described therein and which encodes RAR-α.

(5) Grouping of claims.

Appellant's brief includes a statement that claims 1 to 14, 24 to 34, 39 to 57 and 59 do not stand or fall together and provides reasons as set forth in 37 C.F.R. § 1.192(c)(5) and (c)(6).

(6) Claims appealed.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) Prior Art of record.

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Petkovich, M. et.al. "A human retinoic acid receptor which belongs to the family of nuclear receptors", NATURE, Vol.330, (December 3, 1987), pp. 444 to 450.

Hauptmann, R. et.al. "A novel class of human type I interferons", NUCLEIC ACIDS RESEARCH, Vol.13, No.12, (July, 1985), pp. 4739 to 4749.

Krust, A. et.al. "The chicken receptor sequence: homology with v-erbA and the human oestrogen and glucocorticoid receptors", EMBO Journal, Vol.5, No.3, (May, 1986), pp. 891 to 897.

(8) New prior art.

No new prior art has been applied in this examiner's answer.

(9) Grounds of rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Claims 1 to 14, 24 to 34, 39 to 57 and 59 are rejected under 35 U.S.C. § 103 as being unpatentable over the Petkovich et.al. publication in view of the Hauptmann et.al. and Krust et.al. publications. These claims are drawn to an isolated DNA encoding a retinoic acid nuclear receptor protein, defined fragments of that DNA, a vector containing that DNA, a cell containing that vector, and a process of using that DNA to detect related DNAs in a sample. It should be noted that the claimed DNA corresponds to

DNA which defines the insertion site of the hepatitis B virus in a human hepatoma, which is why it was originally claimed as a DNA encoding the hap gene product.

The Petkovich et.al. publication, in its entirety, described an isolated DNA encoding a retinoic acid nuclear receptor protein prior to the instant invention and which was designated hRAR and which is currently referred to as RAR-α. This reference disclosed, under the section titled **Related human genomic sequence** on page 448 that "[t]here is a remarkable identity between the N-terminal half of region C of hRAR and an amino-acid sequence encoded in a DNA segment located immediately downstream from the insertion site of the hepatitis B virus (HBV) genome in a human hepatoma." This reference refers to the gene product of this insertion site as hORF and further states that "[i]t is striking that the deduced amino-acid sequence of this putative finger of hORF is identical to that of hRAR, and that this homology extends further upstream up to amino acid 31 of hRAR, but ceases abruptly after amino acid 79, where there is a putative splicing donor site (underlined in Fig. 3c) in the hORF genomic DNA." This reference further disclosed that the hORF gene was known to be located on chromosome 3 whereas the hRAR gene was located on chromosome 17 and shows that at least 200 bases of the nucleotide sequence of the claimed DNA as well as 70 consecutive amino acid residues of the encoded protein had been described in the art prior to the instant invention as shown by

Figure 3c of this reference. In summary, the Petkovich et.al. publication described an isolated DNA encoding hRAR which is structurally related to the protein encoded by the claimed DNA, disclosed the chromosomal location and partial nucleotide sequence of the human gene corresponding to the claimed DNA (encoding hORF a.k.a. RAR-ß) and reasonably speculated that hORF probably encodes a retinoic acid or retinol receptor, based upon the available evidence which included the 100% amino acid sequence identity between the N-terminal halves of the C regions of the encoded products hRAR (RAR-α) and hORF (RAR-ß). The Petkovich et.al. reference differs from the instant invention because it did not disclose a DNA encoding the entire hORF product described therein, and additional fragments thereof.

The Hauptmann et.al. and Krust et.al. publications have been relied upon to exemplify the skill of an artisan at the time of the instant invention. These references show that the isolation of a DNA encoding one protein by screening a suitable DNA library with a DNA encoding a structurally related protein was routine in the art at the time that the instant invention was made, as was the construction of expression vectors and transformed cells containing such vectors.

The isolation of a DNA encoding the hORF gene product described in the Petkovich et.al. reference by screening a liver cDNA library with either the DNA encoding hRAR or a DNA encoding part of the hORF product by those methods exemplified here by the

Hauptmann et.al. and Krust et.al. publications would have been obvious to an artisan of ordinary skill at the time of the instant invention. An artisan of molecular biology would have specifically chosen a liver cDNA library because this is the tissue in which EBV was known to be most infectious and was the tissue from which the Hap cell line was derived.

(10) New ground of rejection.

This Examiner's Answer does not contain any new ground of rejection.

(11) Response to argument.

Appellant has presented a argument that appears to be based upon a pretext that they created the nucleotide sequence of the claimed DNA and the amino acid sequence of the encoded protein. This is incorrect. The sequence of the claimed DNA and encoded protein is a product of nature and not the result of any contribution by Appellant. Appellant's contribution to the art consists of the isolation of the claimed DNA and the patentability of the instant invention under 35 U.S.C. § 103 is based upon the obviousness of isolating that DNA in view of the prior art. At no point have the pending claims been rejected on a position that an artisan would have found it obvious to alter the DNA described in the Petkovich et.al. publication to arrive at the claimed DNA and, therefore, Appellant's extensive arguments traversing this position are misplaced.

Appellant's allegation that the RAR-ß gene was unknown prior

to Appellant's discovery is incorrect because this gene was known as the hORF gene described in the Petkovich et.al. publication prior to the instant invention, as was stated in the pending rejection. This gene was not only known prior to the instant invention, but had been partially characterized as shown in Figure 3c of the Petkovich et.al. publication which presents both a partial nucleotide sequence of the gene and a partial amino acid sequence of the encoded protein, and further disclosed the chromosomal location of that gene and the possible relatedness of the gene product to a known nuclear retinoic acid receptor. Far from being unknown, the gene corresponding to the claimed DNA had been characterized to such an extent that the isolation of that DNA was the next logical and obvious step in its further characterization. The Petkovich et.al. publication effectively place the claimed DNA in the hands of an artisan of ordinary skill prior to the instant invention.

Claims 4 to 9 and 57 are drawn to specific DNAs which contain defined nucleotide sequences, each of which is a part (fragment) of the nucleotide sequence of the RAR-ß (hORF) gene of the instant invention. Each of the Petkovich et.al. (Figures 3a and 3b) and Krust et.al.(see Figures 3, 4 and the Discussion) publications disclosed that members of the steroid/thyroid hormone family of nuclear receptors, of which hORF was believed to be a member prior to the instant invention, were composed of six recognizable domains and that some of these domains,

specifically regions C and E, tended to have highly conserved amino acid sequences whereas other regions are not. An artisan would have found the construction of a nucleic acid probe corresponding to a non-conserved region of the hORF gene to specifically detect the expression of only that gene by northern hybridization using those methods that were routine in the art, to have been obvious at that time. Conversely, an artisan would have found the construction of a probe corresponding to a conserved region of that gene to permit the detection of related nucleic acids in a sample, as was disclosed in the section titled **Cloning of a receptor-like cDNA** in the Petkovich et.al. publication and in the **Results** section of the Krust et.al. publication, to also have been fairly taught by this combination of references.

Claims 39, 41, 42, 46 to 52, 54 to 56 and 59 are drawn to a DNA corresponding to the hORF gene and including a 5' noncoding region. As shown in Figure 2 of the Petkovich et.al. publication and Figure 12 of the Krust et.al. publication, the isolation of a DNA corresponding to a known gene and/or gene product invariably will also result in the isolation of associated 5' and 3' noncoding regions. Appellant neither discovered nor invented the nucleic acid sequence of the 5' noncoding region of hORF (RAR-ß) and its isolation was obvious for those reasons applied to claims 1 to 3, 10 to 14, 24 to 34, 40, 43 to 45 and 53 above.

For the above reasons, it is believed that the rejections

should be sustained.

Respectfully submitted,

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